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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,470	01/07/2005	Thomas Tuschl	2923-673	5503
6449 7590 09/15/2009 ROTHWELL, FIGG, ERNST & MANBECK, P.C. 1425 K STREET, N.W. SUITE 800 WASHINGTON, DC 20005				
EXAMINER SHIN, DANA H				
ART UNIT 1635		PAPER NUMBER		
NOTIFICATION DATE 09/15/2009		DELIVERY MODE ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

### Office Action Summary

**Application No.**

10/520,470

**Applicant(s)**

TUSCHL ET AL.

**Examiner**

DANA SHIN

**Art Unit**

1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 12 June 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,3-8,11-16,20,22-36 and 38-44 is/are pending in the application.
- 4a) Of the above claim(s) 22-31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,3-8,11-16,20,32-36 and 38-44 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Status of Application/Amendment/Claims***

This Office action is in response to the communications filed on June 12, 2009.

Currently, claims 1, 3-8, 11-16, 20, 22-36, and 38-44 are pending. Claims 22-31 have previously been withdrawn as being drawn to non-elected inventions. Accordingly, claims 1, 3-8, 11-16, 20, 32-36, and 38-44 are under examination on the merits in the instant case.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Response to Arguments and Amendments***

#### **Withdrawn Rejections**

Any rejections not repeated in this Office action are hereby withdrawn.

#### **Maintained Rejections**

#### ***Claim Rejections - 35 USC § 102***

Claims 1, 3-8, 11-16, 20, 32-36, and 38-42 remain rejected under 35 U.S.C. 102(e) as being anticipated by McSwiggen for the reasons of record as set forth in the Office action mailed on March 5, 2009 and for the reasons stated below.

Applicant's arguments filed on June 12, 2009 have been fully considered but they are not persuasive. Applicant argues that the claim amendment reciting "completely" single-stranded is sufficient to overcome this rejection. Contrary to applicant's argument, the claim language "completely" does not differentiate the claimed structure from the structure of the single-stranded siRNA that forms a hairpin secondary structure when entered into a cell of McSwiggen. As clearly recited in the claims, the "completely" single-stranded RNA has a length of 14-50 nucleotides, wherein only 14 (see for example claim 1) or 20 (see for example claim 38) nucleotides at the 5' end are complementary to the target RNA. Hence, the claims inherently indicate that the rest of 15-50 or 16-50 or 30-50 nucleotide positions in the single-stranded RNA may not be complementary to the target RNA, thereby suggesting that the remaining nucleotides at the 3' end can be part of the secondary hairpin loop sequence or the sense sequence of the self-complementary, single-stranded siRNA molecule as taught by McSwiggen. Note that McSwiggen explicitly taught that RNAi-mediating RNA molecules can be prepared as a single-stranded RNA comprising a nucleotide sequence that is capable of forming a self-complementary hairpin double-stranded RNA. See for example paragraph 0027: "The siNA molecule can comprise *a single-strand* having complementary sense and antisense regions." See paragraph 0049: "a siNA molecule of the invention comprises *a single-stranded* hairpin structure". See paragraph 0115: "The siNA can be *a single-stranded* hairpin polynucleotide having self-complementary sense and antisense regions". See claim 30: "one siNA molecule comprises *a single-strand* having complementary sense and antisense regions". (emphasis added). As such, the mere addition of the word "completely" does not make the claimed single-stranded RNA molecule as being incapable of forming a secondary hairpin, double-stranded RNA molecule

when introduced into a cell, in light of the claim language (e.g., only 14 5' nucleotides out of 50 nucleotides are complementary to target) indicating such single-stranded nucleotide structure having both antisense and sense regions. Again, the claims do not identify what the remaining 3' nucleotides do in terms of the "completely" single-stranded RNA molecule and furthermore, the claims do not exclude self-complementary hairpin RNA structure as currently written. In view of the foregoing, this rejection is maintained.

Claims 1, 3-8, 11-16, 20, 32-36, and 38-42 remain rejected under 35 U.S.C. 102(e) as being anticipated by Finney et al. for the reasons of record as set forth in the Office action mailed on March 5, 2009 and for the reasons stated below.

Applicant's arguments filed on June 12, 2009 have been fully considered but they are not persuasive. Applicant argues that the claimed invention is unobvious because Finney et al. do not teach "completely" single-stranded RNA structure because the RNAi molecules of Finney et al. form a hairpin loop structure. Again, as stated hereinabove, the claims do not exclude single-stranded RNA molecules that comprise both antisense and sense sequences in the single-stranded polynucleotide sequence as the claims only require less than half (e.g., 14 out of 50 nucleotides, 20 out of 50 nucleotides) of the single-stranded RNA be complementary to the target sequence. Since applicant has failed to show how the mere addition of the language "completely" excludes single-stranded siRNA molecules having antisense and sense strands that can thus form a self-complementary hairpin siRNA structure in a cell, this rejection is maintained.

**New Rejections Necessitated by Amendment**

**Claim Rejections - 35 USC § 112**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-8, 11-16, 20, 32-36, 38-42, and 44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 1, 3-8, 11-16, 20, 32-36, and 38-42 are currently amended to recite a limitation that was not recited previously, and claim 44 is newly entered claims. Applicant has pointed out the amended claims are supported at page 11, lines 7-20 of the instant application. However, there does not appear to be a written description of the claim limitation “completely single-stranded”, which in the instant case applicant meant to indicate non-self-complementary RNA that only consists of antisense or target complementary sequence. See applicant's remarks on pages 10-11, wherein applicant asserts that the term “completely single-stranded” does not encompass a single stranded RNA that forms a self-complementary RNA duplex. The passage pointed out by applicant describes that a single-stranded RNA has a length of 14-50 nucleotides, preferably 15-29 nucleotides, wherein 14-20 5' most nucleotides are “substantially complementary” to a target transcript. Hence, the passage does suggest that the single-stranded RNA of the invention can comprise non-complementary nucleotide sequences in the 3'

nucleotides as well as the 5' nucleotides. Further, as expressly acknowledged by applicant such that "the language "completely single stranded" is not specifically used in the present application", the entire disclosure of the instant application including page 11 pointed out by applicant does not provide adequate support and written description for the completely single-stranded siRNA that does not form a self-complementary RNA duplex.

Furthermore, with regard to the new claim, claim 44, applicant has not pointed out where the new claims are supported. Claim 44 is directed to a method comprising a completely single-stranded RNA having 15-29 nucleotides wherein at least 15 5' most nucleotides are completely complementary to a target transcript. As stated above, the "completely single-stranded RNA" meant by applicant is an RNA that does not form a self-complementary duplex. However, as explicitly recited, claim 44 does not require that all 15-29 nucleotides are completely complementary to a target transcript; rather it requires that only 15 5' most nucleotides out of 29 total nucleotides are complementary to a target transcript. As such, the instant application as originally filed does not provide adequate support that the claimed "completely single-stranded RNA" unequivocally excludes a single-stranded RNA having both antisense region (5' most nucleotides) and sense region (3' most nucleotides) that form a self-complementary duplex.

Accordingly, the claim limitations in the amended claims and the new claims are considered to introduce new matter which is not adequately described in the application as originally filed.

Claims 43-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting target expression in mammalian cells *in vitro*

with a single-stranded siRNA of at least 19 nucleotides in length, does not reasonably provide enablement for a method using fewer than 19 nucleotides in length within the claimed length range of 15-29 nucleotides. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With respect to previous 103(a) rejections based on Tijsterman et al. (*Science*, 2002), applicant and the declarant (see the declaration filed on October 7, 2008) have stated of record that a short, single-stranded siRNA mediated RNAi in mammalian cells was unpredictable and unknown at the time the invention was made. For example, the declarant expressly stated under Section 1001 of Title 18 of the United States Code that "it would have been hopeless to use short single-stranded RNA molecules for RNAi in mammalian systems". The instant application explicitly demonstrates that single-stranded siRNA of 15 nucleotides or 17 nucleotides in length that fall within the claimed length range of 15-29 nucleotides do not inhibit target expression in mammalian cells compared to a control siRNA. See Figure 11. Given the incomplete knowledge pertaining to the technology based on the RNAi activity in a mammalian system mediated by a single-stranded, short siRNA that is completely complementary to a target transcript at the time the invention was made as acknowledged by applicant, and given the negative teachings pertaining to shorter than 19 nucleotides in length as disclosed by the inventors of the instant application, an undue amount of experiment would have been necessitated for one of ordinary skill in the art at the time the invention was made.

Hence, the instant specification fails to provide enabling disclosure commensurate in scope with the claimed invention.

***Conclusion***

No claim is allowed.

This application contains claims 22-31 drawn to inventions nonelected without traverse in the reply filed on June 4, 2007. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, 7am-3:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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